EXHIBIT O

the current findings are due to bias from health care surveillance. We do not agree with that interpretation. Rather, the consistent findings of our previous studies on squamous cell carcinoma of the skin[2] and lip[3]; our recent study on Merkel cell carcinoma and adnexal skin tumors[4]; and a previous US study on lip cancer[5] are compatible with hydrochlorothiazide use being linked to an increased risk of UV-dependent skin cancers in a dose-dependent manner. This is in line with the suggested biological mechanism of the carcinogenic potential of hydrochlorothiazide, namely the drug's known photosensitizing properties. To that end, it is worth highlighting that we did not find increased risks for any of the skin cancers mentioned here being associated with use of other antihypertensive drugs. In particular, we observed null associations for the closely related thiazide drug bendroflumethiazide even for the risk of squamous cell carcinoma, while the risk of this skin cancer was increased 7-fold in patients with high cumulative use (≥200 000 mg) of hydrochlorothiazide. The likely explanation for this finding is that bendroflumethiazide—although equally photosensitizing as hydrochlorothiazide when compared mole to mole—is typically used in one-tenth the dose as compared with hydrochlorothiazide.

Finally, we respectfully disagree that researchers should abstain from publishing epidemiological studies contingent on their findings. However, future studies are definitely needed to fully elucidate the association of hydrochlorothiazide to melanoma and other skin cancers. Like van den Born and colleagues, we find it imperative that a drug's potential adverse risks are weighed against its established benefits. We have, for the same reason, consistently emphasized that no patients should stop their treatment with hydrochlorothiazide based on our findings. For the time being, we await the results of several ongoing studies as well as the pending recommendation by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee, which is currently evaluating the findings of this and previous similar studies.[6]

Anton Pottegård, MScPharm, PhD
David Gaist, MD, PhD

Author Affiliations: Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark (Pottegård); Department of Neurology, Odense University Hospital, Odense, Denmark (Gaist); Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark (Gaist).

Corresponding Author: Anton Pottegård, MScPharm, PhD, Clinical Pharmacology and Pharmacy, University of Southern Denmark, JB Winsløwsvej 19, 2, 5000 Odense C, Denmark (apottegaard@health.sdu.dk).

Conflict of Interest Disclosures: None reported.

1. Pottegård A, Pedersen SA, Schmidt SAJ, Hölmich LR, Friis S, Gaist D. Association of hydrochlorothiazide use and risk of malignant melanoma. *JAMA Intern Med*. 2018;178(8):1120-1122. doi:10.1001/jamainternmed.2018.1652

2. Pedersen SA, Gaist D, Schmidt SAJ, Hölmich LR, Friis S, Pottegård A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: a nationwide case-control study from Denmark. *J Am Acad Dermatol*. 2018;78(4):673-681. doi:10.1016/j.jaad.2017.11.042

3. Pottegård A, Hallas J, Olesen M, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med*. 2017;282(4):322-331. doi:10.1111/joim.12629

4. Pedersen SA, Johannesdottir Schmidt SA, Hölmich LR, Friis S, Pottegård A, Gaist D. Hydrochlorothiazide use and risk of Merkel cell carcinoma and malignant adnexal skin tumors: a nationwide case-control study [published online June 15, 2018]. *J Am Acad Dermatol*. doi:10.1016/j.jaad.2018.06.014

5. Friedman GD, Asgari MM, Warton EM, Chan J, Habel LA. Antihypertensive drugs and lip cancer in non-Hispanic whites. *Arch Intern Med*. 2012;172(16):1246-1251. doi:10.1001/archinternmed.2012.2754

6. Pharmacoviligance Risk Assessment Committee. Meeting minutes January 8-11, 2018. http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2018/03/WC500244940.pdf. Accessed June 30, 2018.

In Reply In response to the letter from Ippolito and Veuger, our Research Letter[1] provides support for an association between pharmaceutical industry marketing and opioid prescribing by physicians.[2]

First, to establish temporality between exposure and outcome, we lagged physician opioid prescribing from marketing by 1 year.[1] This allowed us to ensure that prescribing changes occurred after marketing was received, thus reducing the likelihood of reverse causality. Analyses also adjusted for prior prescribing behaviors, which likely confound the relationship between marketing and subsequent opioid prescribing.

Second, our findings are consistent with other research[3,4] showing that physicians who receive pharmaceutical industry payments prescribe more of the medications being marketed. Third, like other studies,[3] we found a "dose-response" association between marketing and prescribing, with each additional industry-sponsored meal associated with greater subsequent prescribing.

It is unlikely that pharmaceutical companies would invest so heavily in direct-to-physician marketing if it did not increase or at least maintain current levels of prescribing. Even in the event of reverse causality—that is, that pharmaceutical companies market heavily to physicians who already frequently prescribe opioids (presumably to maintain their own prescribing levels and/or influence other prescribers in their practices)—there remains the public health question of whether such a practice is appropriate amid an opioid overdose epidemic initially fueled in part by the availability of prescription opioids.

Ippolito and Veuger suggest that regulations limiting marketing from pharmaceutical companies would prevent physicians from receiving important information from manufacturers. Manufacturers may indeed offer information on appropriate opioid prescribing. Such information, however, is readily available from other sources, such as medical professional organizations and governmental bodies, and advocates have long argued that physicians should receive education from sources other than the pharmaceutical industry.[5] The experience of academic medical centers that have limited marketing to physicians and trainees suggests that such restrictions reduce the influence of manufacturers on prescribing behaviors as intended.[6]

Legislation to limit industry payments to physicians is under discussion, and some pharmaceutical companies are voluntarily reducing opioid marketing. Much attention has been paid to speaker fees and other payments of larger value. Our finding that the provision of industry-sponsored meals may also influence physician prescribing underscores the importance of limiting the number of marketing interactions with physicians, not just the value of payments.

Scott E. Hadland, MD, MPH, MS
Magdalena Cerdá, DrPH, MPH
Brandon D. L. Marshall, PhD

Author Affiliations: Grayken Center for Addiction, Boston Medical Center, Boston, Massachusetts (Hadland); Division of General Pediatrics, Department of Pediatrics, Boston University School of Medicine, Boston, Massachusetts (Hadland); Department of Emergency Medicine, School of Medicine, University of California, Davis, Sacramento (Cerdá); Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island (Marshall).

Corresponding Author: Scott E. Hadland, MD, MPH, MS, Grayken Center for Addiction, Boston Medical Center, 88 E Newton St, Vose Hall, Room 322, Boston, MA 02118 (scott.hadland@bmc.org).

Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Hadland was supported by the Thrasher Research Fund Early Career Award, the Academic Pediatric Association Young Investigator Award, the Loan Repayment Program Award L40 DA042434 (National Institutes of Health/National Institute on Drug Abuse [NIH/NIDA]), and K23 DA045085 (NIH/NIDA). Dr Cerdá was supported by R01 DA039962 (NIH/NIDA).

Role of the Funder/Sponsor: The sponsors had no role in the preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

1. Hadland SE, Cerdá M, Li Y, Krieger MS, Marshall BDL. Association of pharmaceutical industry marketing of opioid products to physicians with subsequent opioid prescribing. *JAMA Intern Med*. 2018;178(6):861-863. doi:10.1001/jamainternmed.2018.1999

2. Hernán MA. The C-word: scientific euphemisms do not improve causal inference from observational data. *Am J Public Health*. 2018;108(5):616-619. doi:10.2105/AJPH.2018.304337

3. Yeh JS, Franklin JM, Avorn J, Landon J, Kesselheim AS. Association of industry payments to physicians with the prescribing of brand-name statins in Massachusetts. *JAMA Intern Med*. 2016;176(6):763-768. doi:10.1001/jamainternmed.2016.1709

4. DeJong C, Aguilar T, Tseng C-W, Lin GA, Boscardin WJ, Dudley RA. Pharmaceutical industry-sponsored meals and physician prescribing patterns for Medicare beneficiaries. *JAMA Intern Med*. 2016;176(8):1114-1122. doi:10.1001/jamainternmed.2016.2765

5. Tabas JA, Baron RB. Commercial funding of accredited continuing medical education. *BMJ*. 2012;344:e810. doi:10.1136/bmj.e810

6. Larkin I, Ang D, Steinhart J, et al. Association between academic medical center pharmaceutical detailing policies and physician prescribing. *JAMA*. 2017;317(17):1785-1795. doi:10.1001/jama.2017.4039

Reduced Opioid Marketing Could Limit Prescribing Information for Physicians

To the Editor A Research Letter recently published in *JAMA Internal Medicine* by Hadland and colleagues[1] reported on the relationship between pharmaceutical industry marketing of opioid products to physicians in 2014 and the frequency of opioid prescriptions by physicians in 2015. The authors carried out a difference-in-differences analysis to show that among physicians who prescribed opioids in 2015, those who received payments involving opioid products in 2014 had higher opioid prescribing levels in 2015. Hadland and colleagues are forthright in noting that the findings "establish an association, not cause and effect."[1(p863)] While this correlation undoubtedly exists, the authors then concluded that these results support policy changes that only make sense if this correlation also represents a causal link that flows from payments to opioid prescriptions. In particular, Hadland and colleagues recommended "a voluntary decrease or complete cessation of marketing to physicians"[1(p863)] by manufacturers, as well as consideration of "legal limits on the number and amount of payments" by federal and state governments. If the implied causal link does not exist, these measures would merely limit the information and other resources available to physicians without reducing unwarranted opioid prescriptions.

Benedic Ippolito, PhD
Stan Veuger, PhD

Author Affiliations: American Enterprise Institute for Public Policy Research, Washington, DC.

Corresponding Author: Stan Veuger, PhD, American Enterprise Institute for Public Policy Research, 1789 Massachusetts Ave NW, Washington, DC 20010 (stan.veuger@aei.org).

Conflict of Interest Disclosures: None reported.

1. Hadland SE, Cerdá M, Li Y, Krieger MS, Marshall BDL. Association of pharmaceutical industry marketing of opioid products to physicians with subsequent opioid prescribing. *JAMA Intern Med*. 2018;178(6):861-863. doi:10.1001/jamainternmed.2018.1999

In Reply We used the term *lactic acidosis* in the title of our study[1] to be consistent with previous literature and to facilitate study identification.[2] However, our study[1] does not use lactate concentration to define acidosis events. In addition, our study is observational, and the ability to infer causality—even with techniques such as propensity score matching and active comparator analyses—is limited.

With regard to the issue of dose response brought up by Mohammedi and colleagues,[3] our study[1] focused on the risk associated with metformin use within strata of estimated glomerular filtration rate (eGFR) without respect to dose. If we were to separate metformin prescriptions into doses of more than 2 g/d and 2 g/d or less, both dose groups had similar risk of acidosis compared with sulfonylurea use at eGFR greater than 90 mL/min/1.73 m^2, eGFR 60 to 89 mL/min/1.73 m^2, and eGFR 45 to 59 mL/min/1.73 m^2. There were too few people in the group taking more than 2 g/d within the eGFR categories 30 to 44 mL/min/1.73 m^2 and less than 30 mL/min/1.73 m^2 to reliably estimate risk of acidosis for this dosage; the results of the group taking 2 g/d or less were consistent with results in the published study.[1] An earlier cohort study from the United Kingdom found a significantly higher risk of acidosis among patients if their most recently prescribed dose was greater than 2 g/day (adjusted hazard ratio, 6.4; 95% CI, 1.35-30.3), but the higher risk was not significant among those prescribed 2 g/day or less (adjusted hazard ratio, 3.78; 95% CI, 0.9-15.8).[4]

Benjamin Lazarus, MBBS, MPH
Jung-Im Shin, MD, PhD
Morgan E. Grams, MD, PhD

Author Affiliations: Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Lazarus, Shin, Grams); Division of Nephrology, Monash Medical Centre, Clayton, Australia (Lazarus); Department of Medicine, Johns Hopkins University, Baltimore, Maryland (Grams).

Corresponding Author: Morgan E. Grams, MD, PhD, Department of Medicine, Johns Hopkins University, 2024 E Monument Street, Baltimore, MD, 21205 (mgrams2@jhmi.edu).

Conflict of Interest Disclosures: None reported.